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Evaluation and Improvement of the National Early Warning Score (NEWS2) for COVID-19: a multi-hospital study

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Abstract

Background	The National Early Warning Score (NEWS2) is currently recommended in the United Kingdom for risk-stratification of COVID-19 patients, but little is known about its ability to detect severe cases. We aimed to evaluate NEWS2 for prediction of severe COVID-19 outcome and identify and validate a set of blood and physiological parameters routinely-collected at hospital admission to improve upon use of NEWS2 alone for medium-term risk stratification.
Methods	Training cohorts comprised 1276 patients admitted to King's College Hospital National Health Service (NHS) Foundation Trust with COVID-19 disease from 1 st March to 30 th April 2020. External validation cohorts included 6237 patients from five UK NHS Trusts (Guys and St Thomas' Hospitals, University Hospitals Southampton, University Hospitals Bristol and Weston NHS Foundation Trust, University College London Hospitals, University Hospitals Birmingham), one hospital in Norway (Oslo University Hospital), and two hospitals in Wuhan, China (Wuhan Sixth Hospital and Taikang Tongji Hospital). The outcome was severe COVID-19 disease (transfer to intensive care unit (ICU) or death) at 14 days after hospital admission. Age, physiological measures, blood biomarkers, sex, ethnicity and comorbidities (hypertension, diabetes, cardiovascular, respiratory and kidney diseases) measured at hospital admission were considered in the models.
Results	A baseline model of 'NEWS2 + age' had poor-to-moderate discrimination for severe COVID-19 infection at 14 days (area under receiver operating characteristic curve (AUC) in training cohort = 0.700; 95% Confidence Interval (CI): 0.680, 0.722; Brier score = 0.192; 95% CI: 0.186, 0.197). A supplemented model adding eight routinely-collected blood and physiological parameters (supplemental oxygen flow rate, urea, age, oxygen saturation, C-reactive protein, estimated glomerular filtration rate, neutrophil count, neutrophil/lymphocyte ratio) improved discrimination (AUC = 0.735; 95% CI: 0.715, 0.757) and these improvements were replicated across seven UK and non-UK sites. However, there was evidence of miscalibration with the model tending to underestimate risks in most sites.
Conclusions	NEWS2 score had poor-to-moderate discrimination for medium-term COVID-19 outcome which raises questions about its use as a screening tool at hospital admission. Risk stratification was improved by including readily available blood and physiological parameters measured at hospital admission, but there was evidence of miscalibration in external sites. This highlights the need for a better understanding of the use of early warning scores for COVID.

Keywords: NEWS2 score, blood parameters, COVID-19, prediction model.

KEY MESSAGES

- The National Early Warning Score (NEWS2), currently recommended for stratification of severe COVID-19 disease in the United Kingdom, showed poor-to-moderate discrimination for medium-term outcomes (14-day transfer to intensive care unit (ICU) or death) among COVID-19 patients.
- Risk stratification was improved by the addition of routinely-measured blood and physiological parameters routinely at hospital admission (supplemental oxygen, urea, oxygen saturation, C-reactive protein, estimated glomerular filtration rate, neutrophil count, neutrophil/lymphocyte ratio) which provided moderate improvements in a risk stratification model for 14-day ICU/death.
- This improvement over NEWS2 alone was maintained across multiple hospital trusts but the model tended to be miscalibrated with risks of severe outcomes underestimated in most sites.
- We benefited from existing pipelines for informatics at King's College Hospital such as CogStack that allowed rapid extraction and processing of electronic health records. This methodological approach provided rapid insights and allowed us to overcome the complications associated with slow data centralisation approaches.

BACKGROUND

As of 9th December 2020, there have been >67 million confirmed cases of COVID-19 disease worldwide[1]. While approximately 80% of infected individuals have mild or no symptoms[2], some develop severe COVID-19 disease requiring hospital admission. Within the subset of those requiring hospitalisation, early identification of those who deteriorate and require transfer to an intensive care unit (ICU) for organ support or may die is vital.

Currently available risk scores for deterioration of acutely-ill patients include (i) widely-used generic ward-based risk indices such as the National Early Warning Score (NEWS2)[3], (ii) the Modified Sequential Organ Failure Assessment (mSOFA)[4] and Quick Sequential Organ Failure Assessment[5] scoring systems; and (iii) the pneumonia-specific risk index, CURB-65[6] which combines physiological observations with limited blood markers and comorbidities. NEWS2 is a summary score of six physiological parameters or ‘vital signs’ (respiratory rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness, temperature and supplemental oxygen dependency) used to identify patients at risk of early clinical deterioration in the United Kingdom (UK) National Health Service (NHS) hospitals[7, 8] and primary care. Some components (in particular, patient temperature, oxygen saturation and supplemental oxygen dependency) have been associated with COVID-19 outcomes[2], but little is known about their predictive value for COVID-19 disease severity in hospitalised patients[9]. Additionally, a number of COVID-19-specific risk indices are being developed[10, 11] as well as unvalidated online calculators[12] but generalisability is unknown[13]. A Chinese study has suggested a modified version of NEWS2 with addition of age only[14] but without any data on performance. With near universal usage of NEWS2 in UK NHS Trusts since March 2019[15], a minor adaptation to NEWS2 would be relatively easy to implement.

As the SARS-Cov2 pandemic has progressed a number of risk prediction models to support clinical decisions, triage and care in hospitalised patients have been proposed[13] incorporating potentially useful blood biomarkers[2, 16–19]. These include neutrophilia and lymphopenia, particularly in older adults[11, 18, 20, 21], neutrophil-to-lymphocyte ratio[22], C-reactive Protein (CRP) [13] and lymphocyte-to-CRP ratio[22], markers of liver and cardiac injury such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cardiac troponin[23] and elevated D-dimers, ferritin and fibrinogen [2, 6, 8].

Our aim is to evaluate the NEWS2 score and identify which clinical and blood biomarkers routinely measured at hospital admission can improve medium-term risk stratification of severe COVID-19 outcome at 14 days from hospital admission. Our specific objectives were:

- 1 To explore independent associations of routinely measured physiological and blood parameters (including NEWS2 parameters) at hospital admission with disease severity (ICU admission or death at 14 days from hospital admission), adjusting for demographics and comorbidities;
- 2 To develop a prediction model for severe COVID-19 outcomes at 14 days combining multiple blood and physiological parameters.
- 3 To compare the discrimination, calibration and clinical utility of the resulting model with NEWS2 score and age alone using (i) internal validation; (ii) external validation at seven UK and international sites.

A recent systematic review found that most existing prediction models for COVID-19 had high risk of bias due to non-representative samples, model overfitting, or poor reporting[13]. The analyses presented here build upon our earlier work[24] which suggested that adding age

and common blood biomarkers to the NEWS2 score could improve risk stratification in patients hospitalized with COVID-19. While incorporating external validation, this preliminary work was limited in that the training sample comprised 439 patients (the cohort available at the time of model development). In the present study we (i) expand the cohort used for model development to all 1276 patients at King's College Hospital (KCH); (ii) use hospital admission (rather than symptom onset) as the index date; (iii) consider shorter-term outcomes (3-day ICU/death); (iv) improving the reporting of model calibration and clinical utility; and (v) increase the number of external sites from three to seven.

METHODS

Study cohorts

The KCH training cohort (n=1276) was defined as all adult inpatients testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) by reverse transcription polymerase chain reaction (RT-PCR) between 1st March to 31st April 2020 at two acute hospitals (King's College Hospital and Princess Royal University Hospital) in South East London (UK) of Kings College Hospital NHS Foundation Trust (KCH). All patients included in the study had symptoms consistent with COVID-19 (e.g. cough, fever, dyspnoea, myalgia, delirium, diarrhoea). For external validation purposes we used seven cohorts:

- 1 Guys and St Thomas' Hospital NHS Foundation Trust (GSTT) of 988 cases (3rd March 2020 to 26th August 2020)
- 2 University Hospitals Southampton NHS Foundation Trust (UHS) of 633 cases (7th March to 6th June 2020)
- 3 University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) of 190 cases (12th March to 11th June 2020)

- 4 University College Hospital London (UCH) of 411 cases (1st February to 30th April 2020).
- 5 University Hospitals Birmingham (UHB) of 1037 cases (1st March to 31st June 2020).
- 6 Oslo University Hospital (OUH) of 163 cases (6th March to 13th June 2020).
- 7 Wuhan Sixth Hospital and Taikang Tongji Hospital of 2815 cases (4th February 2020 to 30th March 2020).

Data were extracted from structured and/or unstructured components of electronic health records (EHR) in each site as detailed below.

Measures

Outcome. For all sites, the outcome was severe COVID-19 disease at 14 days following hospital admission, categorised as transfer to ICU/death (WHO-COVID-19 Outcomes Scales 6-8) vs. not transferred to ICU/death (Scales 3-5) [25]. For nosocomial patients (patients with symptom onset after hospital admission) the endpoint was defined as 14 days after symptom onset. Dates of hospital admission, symptom onset, ICU transfer and death were extracted from electronic health records or ascertained manually by a clinician.

Blood and physiological parameters. We included blood and physiological parameters that were routinely obtained at hospital admission which are routinely available in a wide range of national and international hospital and community settings. Measures available for fewer than 30% of patients were not considered (including Troponin-T, Ferritin, D-dimers and glycated haemoglobin (HbA1c), Glasgow Coma Scale score). We excluded creatinine since this parameter correlates highly ($r > 0.8$) with, and is used in the derivation of, estimated glomerular filtration rate. We excluded white blood cell count (WBCs) which is highly correlated with neutrophil and lymphocyte counts.

The candidate blood parameters therefore comprised: albumin (g/L), C-reactive protein (CRP; mg/L), estimated Glomerular Filtration Rate (GFR; mL/min), Haemoglobin (g/L), lymphocyte count ($\times 10^9/\text{L}$), neutrophil count ($\times 10^9/\text{L}$), and platelet count (PLT; $\times 10^9/\text{L}$), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-CRP ratio[22], and urea (mmol/L). The candidate physiological parameters included the NEWS2 total score, as well as the following parameters: respiratory rate (breaths per minute), oxygen saturation (%), supplemental oxygen flow rate (L/min), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), heart rate (beats/min), temperature ($^{\circ}\text{C}$), and consciousness (Glasgow Coma Scale; GCS). For all parameters we used the first available measure up to 48 hours following hospital admission.

Demographics and comorbidities. Age, sex, ethnicity and comorbidities were considered. Self-defined ethnicity was categorised as White vs. non-White (Black, Asian, or other minority ethnic) and patients with ethnicity recorded as ‘unknown/mixed/other’ were excluded (n=316; 25%). Binary variables were derived for comorbidities: hypertension, diabetes, heart disease (heart failure and ischemic heart disease), respiratory disease (asthma and chronic obstructive pulmonary disease (COPD)) and chronic kidney disease.

Data Processing

King's College Hospital

Data were extracted from the structured and unstructured components of the electronic health record (EHR) using natural language processing (NLP) tools belonging to the CogStack ecosystem[26], namely MedCAT[27] and MedCATTrainer[28]. The CogStack NLP pipeline captures negation, synonyms, and acronyms for medical SNOMED-CT (Systematised Nomenclature of Medicine Clinical Terms) concepts as well as surrounding linguistic context

using deep learning and long short-term memory networks. MedCAT produces unsupervised annotations for all SNOMED-CT concepts (Additional file 1: Table S1) under parent terms Clinical Finding, Disorder, Organism, and Event with disambiguation, pre-trained on MIMIC-III[29]. Starting from our previous model[30], further supervised training improved detection of annotations and meta-annotations such as experiencer (is the annotated concept experienced by the patient or other), negation (is the concept annotated negated or not) and temporality (is the concept annotated in the past or present) with MedCATTrainer. Meta-annotations for hypothetical, historical and experiencer were merged into “Irrelevant” allowing us to exclude any mentions of a concept that do not directly relate to the patient currently. Performance of the NLP pipeline for comorbidities mentioned in the text was evaluated on 4343 annotations in 146 clinical documents by a clinician (JT). F1 scores, precision, and recall are presented in Additional file 2: Table S2.

Guy's and St Thomas NHS Foundation Trust (GSTT)

Electronic health records from all patients admitted to Guy's and St Thomas NHS Foundation Trust who had a positive COVID-19 test result between the 3rd of March and 21st of May 2020, inclusive, were identified. Data were extracted using structured queries from six complementary platforms and linked using unique patient identifiers. Data processing was performed using Python 3.7 [31]. The process and outputs were reviewed by a study clinician.

University Hospitals Southampton (UHS)

Data were extracted from the structured components of the UHS CHARTS EHR system and data warehouse. Data was transformed to the required format for validation purposes using Python 3.7 [31]. Diagnosis and comorbidity data of interest were gathered from ICD-10

(International Statistical Classification of Diseases) coded data. No unstructured data extraction was required for validation purposes. The process and outputs were reviewed by an experienced clinician prior to analysis.

University Hospitals Bristol and Weston NHS Foundation Trust (UHBW)

Data were extracted from UHBW electronic health records system (Medway). ICD-10 codes were used for diagnosis and comorbidity data. Data were transformed in line with project specifications and exported for analysis in Python 3.7 [31].

University College Hospital London (UCH)

Dates of hospital admission, symptom onset, ICU transfer and death were extracted from electronic health records. The outcome (14 day ICU/death) was defined in UCLH as “initiation of ventilatory support (continuous positive airway pressure, non-invasive ventilation, high flow nasal cannula oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation) or death” which is consistent WHO-COVID-19 Outcomes Scales 6-8.

Wuhan cohort

Demographic, premorbid conditions, clinical symptoms or signs at presentation, laboratory data, treatment and outcome data were extracted from electronic medical records using a standardised data collection form by a team of experienced respiratory clinicians, with double data checking and involvement of a third reviewer where there was disagreement. Anonymised data was entered into a password-protected computerised database.

University Hospitals Birmingham (UHB)

Dates of hospital admission, symptom onset, ICU transfer and death were extracted from electronic health records using the Prescribing Information and Communications System (PICS) system. The extracted data was transformed to the required format for validation purposes using Python 3.8 [31]. Diagnosis and comorbidity data of interest were gathered from ICD-10 coded data. The outcomes (3 and 14 day ICU/death) were defined consistent with WHO-COVID-19 Outcomes Scales 6-8.

Oslo University Hospital (OUH)

All admitted patients with confirmed COVID-19 by positive SARS-CoV2 PCR were included in a quality registry. Data input into the register was manual. Register data was supplemented with test results from the laboratory information system (LIS) by matching exported Excel files from the register with exported Excel files from LIS. The fidelity of the match was checked against the original data source manually for a small number of patients. Only patients with symptoms consistent with COVID-19 were included in the study.

Statistical analyses

All continuous parameters were winsorized (at 1% and 99%) and scaled (mean = 0; standard deviation = 1) to facilitate interpretability and comparability[32]. Logarithmic or square-root transformations were applied to skewed parameters. To explore independent associations of blood and physiological parameters with 14-day ICU/death (Objective 1) we used logistic regression with Firth's bias reduction method[33]. Each parameter was tested independently, adjusted for age and sex (Model 1) and then additionally adjusted for comorbidities (Model 2). *P*-values were adjusted using the Benjamini-Hochberg procedure to keep the False Discovery Rate (FDR) at 5%[34].

To evaluate NEWS2 and identify parameters that could improve prediction of severe COVID-19 outcomes (Objectives 2 and 3) we used regularized logistic regression with a LASSO (Least Absolute Shrinkage and Selection Operator) estimator that shrinks parameters according to their variance, reduces overfitting, and enables automatic variable selection[35]. The optimal degree of regularization was determined by identifying a tuning parameter λ using cross-validation. To avoid overfitting and to reduce the number of false positive predictors, λ was selected to give a model with area under the receiver operating characteristic curve (AUC) one standard error below the ‘best’ model. To evaluate the predictive performance of our model on new cases of the same underlying population (internal validation), we performed nested cross-validation (10 folds for inner loop; 10 folds/1000 repeats for outer loop). Discrimination was assessed using AUC and Brier score. Missing feature information was imputed using k-Nearest Neighbours (kNN) imputation (k=5). All steps (feature selection, winsorizing, scaling, and kNN imputation) were incorporated within the model development and selection process to avoid data leakage that would otherwise result in optimistic performance measures[36]. All analyses were conducted with Python 3.8 [31] using the statsmodels[37] and Scikit-Learn[38] packages.

We evaluated the transportability of the derived regularized logistic regression model in external validation samples from GSTT (n=988), UHS (n=633), UHBW (n=190), UCH (n=411), UHB (n=1037), OUH (n=163), and Wuhan (n=2815). Validation used LASSO logistic regression models trained on the KCH training sample, with code and pre-trained models shared via GitHub¹. Models were assessed in terms of discrimination (AUC, sensitivity, specificity, Brier score), calibration, and clinical utility (decision curve analysis, number needed to evaluate)[32, 39]. Moderate calibration was assessed by plotting model

¹ <https://github.com/ewancarr/NEWS2-COVID-19>

predicted probabilities (x-axis) against observed proportions (y-axis) with LOESS (locally estimated scatterplot smoothing) and logistic curves[40]. Clinical utility was assessed using decision curve analysis where ‘net benefit’ was plotted against a range of threshold probabilities. Unlike diagnostic performance measures, decision curves incorporate preferences of the clinician and patient. The threshold probability (p_t) is where the expected benefit of treatment is equal to the expected benefit of avoiding treatment[41]. Net benefit was calculated by counting the number of true positives (predicted risk $> p_t$ and experienced severe COVID-19 outcome) and false positives (predicted risk $> p_t$ but did not experience severe COVID-19 outcome), and using the below formula:

$$\text{Net benefit} = \frac{\text{True positives}}{N} - \frac{\text{False positives}}{N} \times \frac{p_t}{1 - p_t}$$

Our model was developed as a screening tool, to identify at hospital admission patients at risk of more severe outcomes. The intended treatment for patients with a positive result from this model would be further examination by a clinician, who would make recommendations regarding appropriate treatment (e.g. earlier transfer to ICU, intensive monitoring, treatment). We compared the decision curve from our model to two extreme cases of ‘treat none’ and ‘treat all’. The ‘treat none’ (i.e. routine management) strategy implies that no patients would be selected for further examination by a clinician; the ‘treat all’ strategy (i.e. intensive management) implies that all patients would undergo further assessment. A model is clinically beneficial if the model-implied net benefit is greater than either the ‘treat none’ or ‘treat all’ strategies.

Since the intended strategy involves further examination by a clinician, and is therefore low risk, our emphasis throughout is on avoiding false negatives (i.e. failing to detect a severe

case) at the expense of false positives. We therefore used thresholds of 30% and 20% (for 14-day and 3-day outcomes, respectively) to calculate sensitivity and specificity. This gave a better balance of sensitivity vs. specificity and reflected the clinical preference to avoid false negatives for the proposed screening tool.

Sensitivity analyses

We conducted five sensitivity analyses. First, to explore the ability of NEWS2 to predict shorter-term severe COVID-19 outcome we developed models for ICU transfer/death at 3 days following hospital admission. All steps described above were repeated, including training (feature selection) and external validation. Second, following recent studies suggesting sex differences in COVID-19 outcome[18] we tested interactions between each physiological and blood parameter and sex using likelihood-ratio tests. Third, we repeated all models with adjustment for ethnicity in the subset of individuals with available data for ethnicity (n=960 in the KCH training sample). Fourth, to explore differences between community-acquired vs. nosocomial infection, we repeated all models after excluding 153 nosocomial patients (n=1123). Finally, we considered an alternative baseline model of ‘NEWS2 only’. Our primary analyses used a baseline model of ‘NEWS2 + age’ because NEWS2 is rarely used in isolation for prognostication and treatment decisions will incorporate other patient characteristics such as age.

RESULTS

Descriptive analyses

The KCH training cohort comprised 1276 patients admitted with a confirmed diagnosis of COVID-19 (from 1st March to 31st April 2020) of whom 389 (31%) and were transferred to ICU or died within 14 days of hospital admission, respectively. The validation cohorts

comprised 6237 patients across seven sites. At UK NHS trusts, 30% to 42% of patients were transferred to ICU or died within 14 days of admission. Disease severity was lower in the Wuhan sample, where 4% were transferred to ICU or died. Table 1 presents the demographic and clinical characteristics of the training and validation cohorts. The UK sites were similar in terms of age and sex, with patients tending to be older (median age 59-74) and male (58% to 63%) but varied in the proportion of patients of non-White ethnicity (from 10% at UHS to 40% at KCH and UCH). Blood and physiological parameters were broadly consistent across UK sites.

(TABLE 1 about here)

Logistic regression models were used to assess independent associations between each variable and severe COVID-19 outcome (ICU transfer/death) in the KCH cohort. Additional file 3: Table S3 presents odds ratios adjusted for age and sex (Model 1) and comorbidities (Model 2), sorted by effect size. Increased odds of transfer to ICU or death by 14 days were associated with NEWS2 score, oxygen flow rate, respiratory rate, CRP, neutrophil count, urea, neutrophil/lymphocyte ratio, heart rate, and temperature. Reduced odds of severe outcomes were associated with lymphocyte/CRP ratio, oxygen saturation, estimated GFR, and Albumin.

Evaluating NEWS2 score for prediction of severe COVID-19 outcome

Logistic regression models were used to evaluate a baseline model containing hospital admission NEWS2 score and age for prediction of severe COVID-19 outcomes at 14 days. Internally validated discrimination for the KCH training sample was moderate (AUC = 0.700; 95% Confidence Interval (CI): 0.680, 0.722; Brier score = 0.192; 0.186, 0.197; Table 2). Discrimination remained poor-to-moderate in UK validation sites (AUC = 0.623 to

0.729), but was moderate-to-good in Norway (AUC = 0.786) and Wuhan hospitals (AUC = 0.815) (Figures 1 and 2). Calibration was inconsistent with risks underestimated in some sites (UHS, GSTT) and overestimated in others (UHBW, UHB; Figure 2).

Table 2: KCH internally validated predictive performance (n=1276) based on nested repeated cross-validation

		NEWS2 + age Mean (95% CI)	All features Mean (95% CI)
14-day ICU/death	AUC	0.700 [0.680, 0.722]	0.735 [0.715, 0.757]
	Brier score	0.192 [0.186, 0.197]	0.183 [0.177, 0.189]
	Sensitivity ¹	0.778 [0.747, 0.815]	0.735 [0.702, 0.772]
	Specificity ¹	0.478 [0.445, 0.509]	0.592 [0.562, 0.621]

Notes.

¹ Calculated at 30% probability threshold. AUC based on repeated, nested cross-validation. (inner loop: 10 folds; outer loop = 10 folds/1000 repeats). Missing values imputed at each outer loop with k-Nearest Neighbours (kNN) imputation.

Supplementing NEWS2 with routinely collected blood and physiological parameters

We considered whether routine blood and physiological parameters could improve risk stratification for medium-term COVID-19 outcome (ICU transfer/death at 14 days). When adding demographic, blood, and physiological parameters to NEWS2, nine features were retained following LASSO regularisation, in order of effect size: NEWS2 score, supplemental oxygen flow rate, urea, age, oxygen saturation, CRP, estimated GFR, neutrophil count, neutrophil/lymphocyte ratio. Notably, comorbid conditions were not retained when added in subsequent models, suggesting most of the variance explained was already captured by the included parameters. Internally validated discrimination in the KCH training sample was moderate (AUC = 0.735; 95% CI: 0.715, 0.757) but improved compared to ‘NEWS2 + age’ (Table 3). This improvement over NEWS2 alone was replicated in validation samples (Figure 1). The supplemented model continued to show evidence of substantial miscalibration.

(FIGURE 1 about here)

(FIGURE 2 about here)

Sensitivity analyses

For the 3-day endpoint, 13% of patients at KCH (n=163) and between 16% and 29% of patients in the UK and Norway were transferred to ICU or died (Table 1). The 3-day model retained just two parameters following regularisation: NEWS2 score and supplemental oxygen flow rate. For the baseline model ('NEWS2 + age') discrimination was moderate at internal validation (AUC = 0.764; 95% CI: 0.737, 0.794; Additional file 4: Table S4) and external validation (AUC = 0.673 to 0.755) but calibration remained poor (Additional file 5: Figure S1). Moreover, the supplemented model ('NEWS2 + oxygen flow rate') showed smaller improvements in discrimination compared to those seen at 14 days. For the KCH training cohort internally validated AUC increased by 0.025: from 0.764 (95% CI: 0.737, 0.794) for 'NEWS2 + age' to 0.789 (0.763, 0.819) for the supplemented model ('NEWS2 + oxygen flow rate'). At external validation, improvements were modest (UHBW, OUH) or negative (GSTT) in some sites; but more substantial in others (UHS, UCH). Moreover, model calibration was considerably worse for the supplemented 3-day model (Additional file 5: Figure S1).

We found no evidence of difference by sex (results not shown) and findings were consistent when additionally adjusting for ethnicity in the subset of individuals with ethnicity data and when excluding nosocomial patients (Additional file 6: Table S5). Discrimination for the alternative baseline model of 'NEWS2 only' (Additional file 7: Table S6) showed a similar pattern of results as those for 'NEWS2 + age', except that improvements in discrimination for the supplemented model ('All features') were larger in most sites.

Decision curve analysis

Decision curve analysis for the 14-day endpoint is presented in Figure 3. At KCH the baseline model ('NEWS2 + age') offered small increments in net benefit compared to the 'treat all' and 'treat none' strategies for risk thresholds in the range 25% to 60%. This was replicated in all validation cohorts except for UHBW and OUH where net benefit for 'NEWS2 + age' was lower than the 'treat none' strategy beyond the 40% risk threshold. The supplemented model ('All features') improved upon 'NEWS2 + age' and the two default strategies in most sites across the range 20% to 80%, except for (i) UHBW, where 'treat none' was superior beyond thresholds of 55%; (ii) GSTT, where 'treat all' was superior up to a threshold of 30% and no improvement was seen for supplemented model.

(FIGURE 3 about here)

For the 3-day endpoint the improvement in net benefit for the supplemented model over the two default strategies was smaller, compared to improvements seen at 14 days (Additional file 8: Figure S2). At three sites (UHBW, GSST and Wuhan) neither the baseline ('NEWS2 + age') nor supplemented ('All features') models offered any improvement over the 'treat all' or 'treat none' strategies. At KCH and UHS net benefit for 'NEWS2 + age' was higher than the default strategies for a range of risk thresholds, but was not increased further by the supplemented ('NEWS2 + oxygen flow rate') model.

DISCUSSION

Principal findings

This study is among the first to systematically evaluate NEWS2 for severe COVID-19 outcome and carry out external validation at multiple international sites (five UK NHS Trusts, one hospital in Norway, and two hospitals in Wuhan, China). We found that while

‘NEWS2 + age’ had moderate discrimination for short-term COVID-19 outcome (3-day ICU transfer/death), it showed poor-to-moderate discrimination for medium-term outcome (14-day ICU transfer/death). Thus, while NEWS2 may be effective for short-term (e.g. 24 hours) prognostication, our results question its suitability as a screening tool for medium-term COVID-19 outcome. Risk stratification was improved by adding routinely-collected blood and physiological parameters, and discrimination in supplemented models was moderate-to-good. However, the model showed evidence of miscalibration, with a tendency to underestimate risks in external sites. The derived model for 14-day ICU transfer/death included nine parameters: NEWS2 score, supplemental oxygen flow rate, urea, age, oxygen saturation, CRP, estimated GFR, neutrophil count, neutrophil/lymphocyte ratio. Notably, pre-existing comorbidities did not improve risk prediction and were not retained in the final model. This was unexpected but may indicate that the effect of pre-existing health conditions could be manifest through some of the included blood or physiological markers.

Overall, this study overcomes many of the factors associated with high risk of bias in the development of prognostic models for COVID-19[13] and provides some evidence to support the supplementation of NEWS2 for clinical decisions with these patients.

Comparison with other studies

A systematic review of 10 prediction models for mortality in COVID-19 infection[10] found broad similarities with the features retained in our models, particularly regarding CRP and neutrophil levels. However, existing prediction models suffer several methodological weaknesses including overfitting, selection bias, and reliance on cross-sectional data without accounting for censoring. Additionally, many existing studies have relied on single centre or ethnically homogenous Chinese cohorts, whereas the present study shows validation across

multiple and diverse populations. A key strength of our study is the robust and repeated external validation across national and international sites; however evidence of miscalibration suggests we should be cautious when attempting to generalise these findings. Future research should include larger collaborations and aim to develop ‘from onset’ population predictions.

NEWS2 is a summary score derived from six physiological parameters, including oxygen supplementation. Lack of evidence for NEWS2 use in COVID-19 especially in primary care has been highlighted[9]. The oxygen saturation component of physiological measurements added value beyond NEWS2 total score and was retained following regularisation for 14-day endpoints. This suggests some residual association over and above what is captured by the NEWS2 score, and reinforces Royal College of Physicians guidance that the NEWS2 score ceilings with respect to respiratory function[42].

Cardiac disease and myocardial injury have been described in severe COVID-19 cases in China[2, 23]. In our model, blood Troponin-T, a marker of myocardial injury, had additional salient signal but was only measured in a subset of our cohort at admission, so it was excluded from our final model. This could be explored further in larger datasets.

Strengths and limitations

Our study provides a risk stratification model for which we obtained generalisable and robust results across seven national and international sites with differing geographical catchment and population characteristics. It is among the first to evaluate NEWS2 at hospital admission for severe COVID-19 outcome and among a handful to externally validate a supplemented model across multiple sites.

However, some limitations must be acknowledged. First, there are likely to be other parameters not measured in this study that could substantially improve the risk stratification model (e.g. radiological features, obesity, or comorbidity load). These parameters could be explored in future work but were not considered in the present study to avoid limiting the real-world implementation of the risk stratification model. Second, our models showed better performance in UK secondary care settings among populations with higher rates of severe COVID-19 disease. Therefore, further research is needed to investigate the suitability of our model for primary care settings which have a high prevalence of mild disease severities and in community settings. This would allow us to capture variability at earlier stages of the disease and trends in patients not requiring hospital admission. Third, while external validation across multiple national and international sites represents a key strength, we did not have access to individual participant data and model development was limited to a single site (KCH). Although we benefited from existing infrastructure to support rapid data analysis, we urgently need infrastructure to support data sharing between sites to address some of the limitations of the present study (e.g. miscalibration) and improve the transferability of these models. Not only would this facilitate external validation, but more importantly, it would allow multi-site prediction models to be developed using pooled, individual participant data[43]. Fourth, our analyses would have excluded patients who experienced severe COVID-19 outcome at home or at another hospital, after being discharged from a participating hospital. Fifth, our model was restricted to blood and physiological parameters measured at hospital admission. This was by design and reflected the aim of developing a screening tool for risk stratification at hospital admission. However, future studies should explore the extent to which risk stratification could be improved by incorporating repeated measures of NEWS2 and relevant biomarkers.

CONCLUSIONS

The NEWS2 early warning score is in near-universal use in UK NHS Trusts since March 2019[15] but little is known about its use for COVID-19 patients. Here we showed that NEWS2 and age at hospital admission had moderate discrimination for medium-term (14-day) severe COVID-19 outcome, questioning its use as a tool to guide hospital admission. Moreover, we showed that NEWS2 discrimination could be improved by adding eight blood and physiological parameters (supplemental oxygen flow rate, urea, age, oxygen saturation, CRP, estimated GFR, neutrophil count, neutrophil/lymphocyte ratio) that are routinely collected and readily available in healthcare services. Thus, this type of model could be easily implemented in clinical practice and predicted risk score probabilities of individual patients are easy to communicate. At the same time, although we provided some evidence of improved discrimination versus NEWS2 and age alone, given miscalibration in external sites our proposed model should be used as a complement and not as a replacement for clinical judgment.

DECLARATIONS

Ethics approval and consent to participate

The KCH component of the project operated under London South East Research Ethics Committee (reference 18/LO/2048) approval granted to the King's Electronic Records Research Interface (KERRI); specific work on COVID-19 research was reviewed with expert patient input on a virtual committee with Caldicott Guardian oversight. The UHS validation was performed as part of an urgent service evaluation agreed with approval from trust research leads and the Caldicott Guardian. For UCH, ethical approval was given by East Midlands - Nottingham 2 Research Ethics Committee (REF: 20/EM/0114; IRAS: 282900). The UHB component was operated under the PIONEER Health Data Research Hub in Acute Care ethical approval provided by the East Midlands Derby REC (reference: 20/EM/0158). For UHBW, the project was considered as service evaluation by the organisational review board. Informed consent was deemed unnecessary due to the retrospective observational nature of the data. Ethical approval for GSTT was granted by The London Bromley Research Ethics Committee (reference 20/HRA/1871) to the King's Health Partners Data Analytics and Modelling COVID-19 Group to collect clinically relevant data points from patient's electronic health records. The Wuhan validation was approved by the Research Ethics Committee of Shanghai Dongfang Hospital and Taikang Tongji Hospital. For the OUH validation a project protocol was approved by the Regional Ethical Committee of South-East Norway (Reference number 137045) and the OUH data protection officer (Reference number 20/08822). Informed consent in the OUH cohort was waived because of the strictly observational nature of the project.

Consent for publication

Not applicable.

Availability of data and materials

Code and pre-trained models are available at <https://github.com/ewancarr/NEWS2-COVID-19> and openly shared for testing in other COVID-19 datasets.

Source text from patient records used at all sites in the study will not be available due to inability to safely fully anonymise up to the Information Commissioner Office (ICO) standards and would be likely to contain strong identifiers (e.g. names, postcodes) and highly sensitive data (e.g. diagnoses).

A subset of the KCH dataset limited to anonymisable information (e.g. only SNOMED codes and aggregated demographics) is available on request to researchers with suitable training in information governance and human confidentiality protocols subject to approval by the King's College Hospital Information Governance committee; applications for research access should be sent to kch-tr.cogstackrequests@nhs.net. This dataset cannot be released publicly due to the risk of re-identification of such granular individual level data, as determined by the King's College Hospital Caldicott Guardian.

The GSTT dataset cannot be released publicly due to the risk of re-identification of such granular individual level data, as determined by the Guy's and St. Thomas's Trust Caldicott Guardian.

The UHS dataset cannot be released publicly due to the risk of re-identification of such granular individual level data, as determined by the University Hospital Southampton Caldicott Guardian.

The UCH data cannot be released publicly due to conditions of regulatory approvals that preclude open access data sharing to minimise risk of patient identification through granular individual health record data. The authors will consider specific requests for data sharing as part of academic collaborations subject to ethical approval and data transfer agreements in accordance with GDPR regulations.

The Wuhan dataset used in the study will not be available due to inability to fully anonymise in line with ethical requirements. Applications for research access should be sent to TS and details will be made available via <https://covid.datahelps.life/prediction/>.

The OUH dataset cannot be released publicly due to the risk of re-identification of such granular individual level data.

Competing interests

JTHT received research support and funding from InnovateUK, Bristol-Myers-Squibb, iRhythm Technologies, and holds shares <£5,000 in Glaxo Smithkline and Biogen.

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Authors' contributions

The corresponding author, Dr Ewan Carr, is guarantor of the manuscript.

JT, AMS, RD, EC and RB conceived the study design and developed the study objectives. JT, RD, AF, LR, DB, ZK, TS and AS were the leads to develop CogStack platform. DB, ZK, TS, AS were responsible for the data extraction and preparation. EC, RB, AP, DS contributed to the statistical analyses. All authors contributed to the interpretation of the data. AMS, JT, KO, RZ provided clinical input. All authors contributed to interpret the data, draft the article and provided final approval of the manuscript. DMB, ZK, AS, TS, JTHT, LR, KN performed data processing and software development; KOG, RZ, JTHT performed data validation.

At GSTT, WW and WM were responsible for the data extraction and preparation. WW performed the model validation. AD and VC contributed to the interpretation of the data.

At UHS, MS and FB were responsible for the data extraction and preparation. MS, HP and AS contributed to the statistical analysis. All authors contributed to the interpretation of the data. MS and AP provided clinical input. MS and HP performed data/model validation.

At UCH, RKG and MN were responsible for data extraction and preparation and model validation.

At UHBW, MR and MW were responsible for data extraction and preparation. CM and CB conducted the data and model validation.

For the Wuhan cohort, XZ, XW and JS extracted the data from the EHR system. HW and HZ preprocessed the raw data and conducted the prediction model validations. BG, HW, HZ, TS and JS interpreted the data and results.

At UHB/UoB, UHB IT and AK were responsible for the data extraction and preparation. AK, LS, VRC and GVG performed the model validation. AK, GVG and SB contributed to the interpretation of the data.

At OUH, KW, EKA and ARH were responsible for the data extraction and preparation. AKL contributed to the statistical analysis and performed model validation. All authors contributed to the interpretation of the data.

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FIGURE LEGENDS

Figure 1: Improvement in area under the curve (AUC) for supplemented NEWS2 model for 14-day ICU/death at training and validation sites

Figure 2: Calibration (logistic and LOESS curves) of supplemented NEWS2 model for 14-day ICU/death model at validation sites

Figure 3: Net benefit of supplemented NEWS2 model for 14-day ICU/death compared to default strategies ('treat all' and 'treat none') at training and validation sites

ADDITIONAL FILES

Additional file 1. Table S1: SNOMED terms

Additional file 2. Table S2: F1, precision and recall for NLP comorbidity detection

Additional file 3. Table S3: Logistic regression models for each blood and physiological measure tested separately in the KCH training cohort, for 14- and 3-day ICU/death

Additional file 4. Table S4: Internally validated discrimination for KCH training sample based on nested repeated cross-validation

Additional file 5. Figure S1: Calibration (logistic and LOESS curves) of supplemented NEWS2 model for 3-day ICU/death model at validation sites

Additional file 6. Table S5: Univariate logistic regression models for sensitivity analyses showing odds ratios of ICU/death at 3- and 14-days for subsets of the training cohort

Additional file 7. Table S6: Discrimination for all models in training and validation cohorts, including alternative baseline model of 'NEWS2 only'.

Additional file 8. Figure S2: Net benefit of supplemented NEWS2 model for 3-day ICU/death compared to default strategies ('treat all' and 'treat none') at training and validation sites

Figure 2. Improvement in area under the curve (AUC) for supplemented NEWS2 model for 14-day ICU/death at training and validation sites

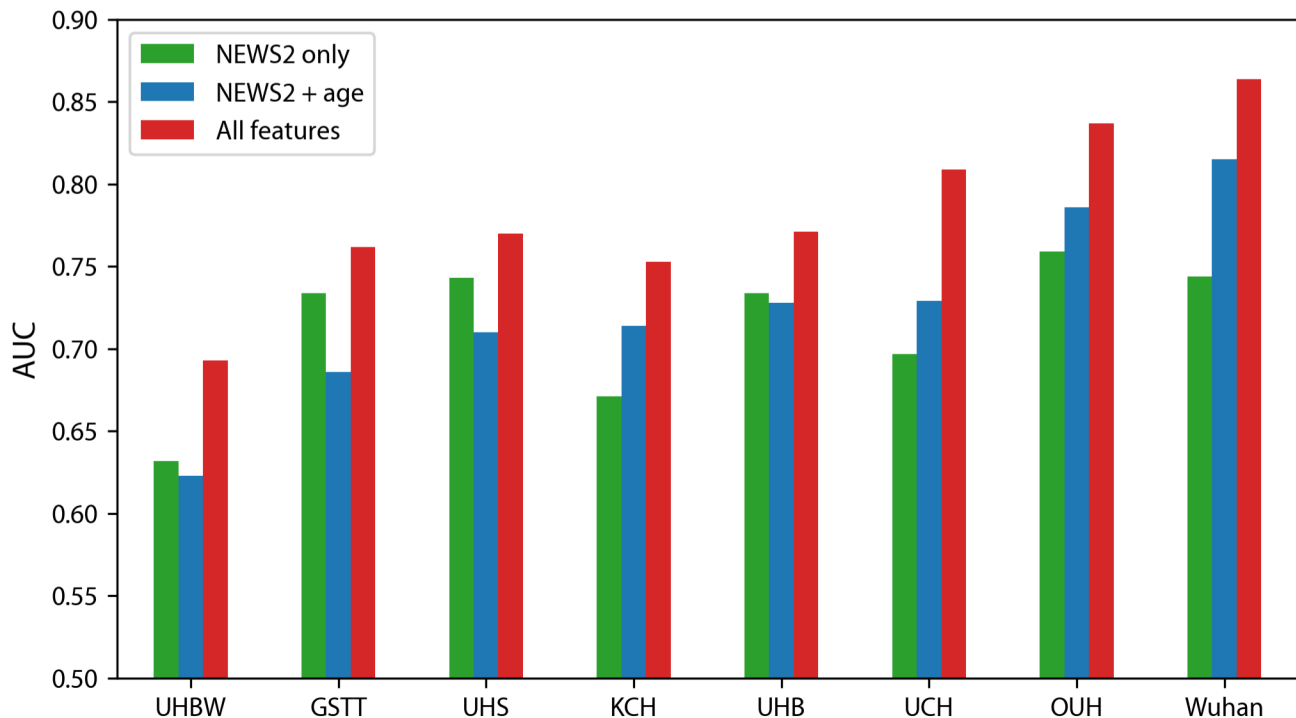


Figure 2. Calibration (logistic and LOESS curves) of supplemented NEWS2 model for 14-day ICU/death model at validation sites

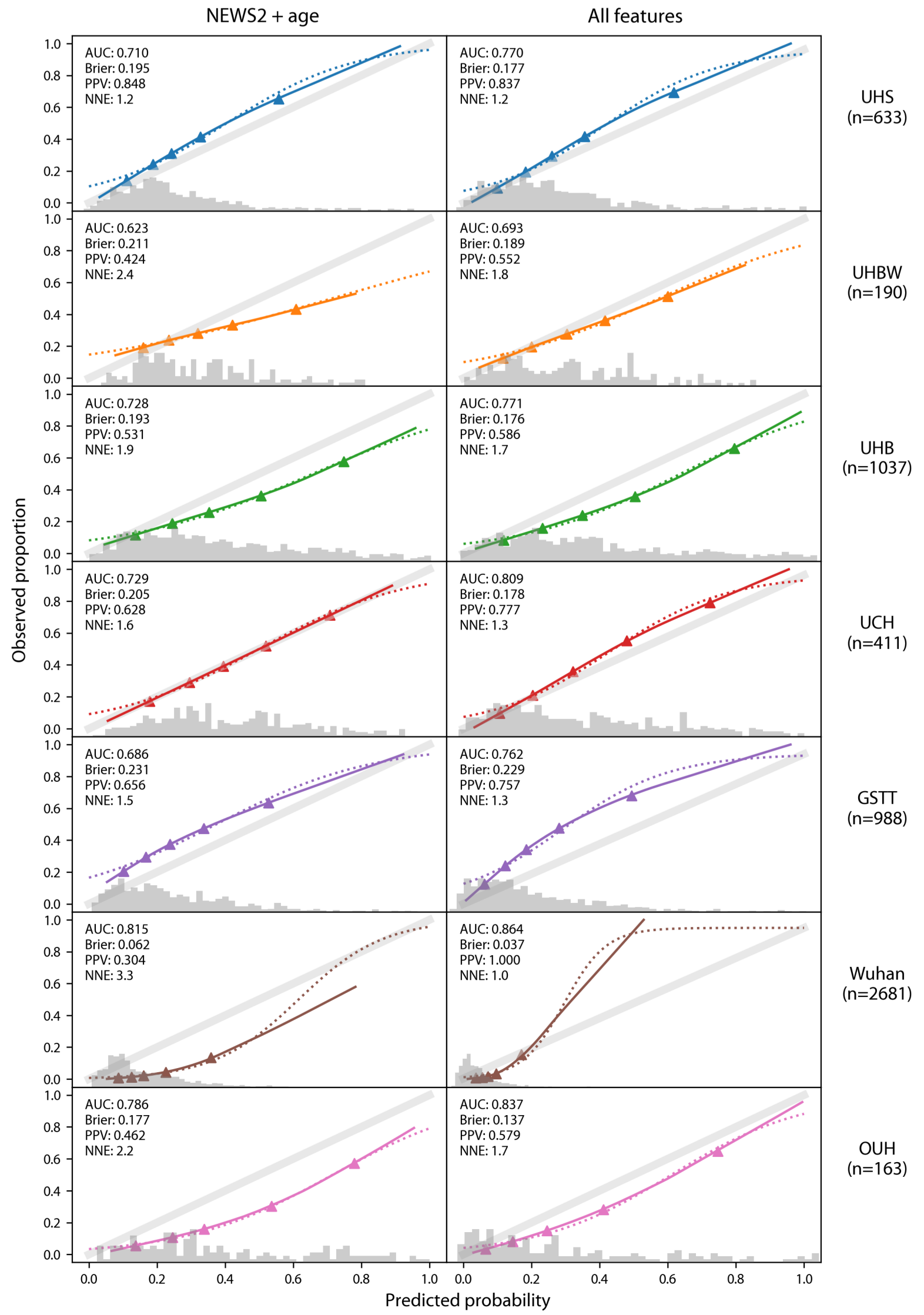


Figure 3. Net benefit of supplemented NEWS2 model for 14-day ICU/death compared to default strategies ('treat all' and 'treat none') at training and validation sites

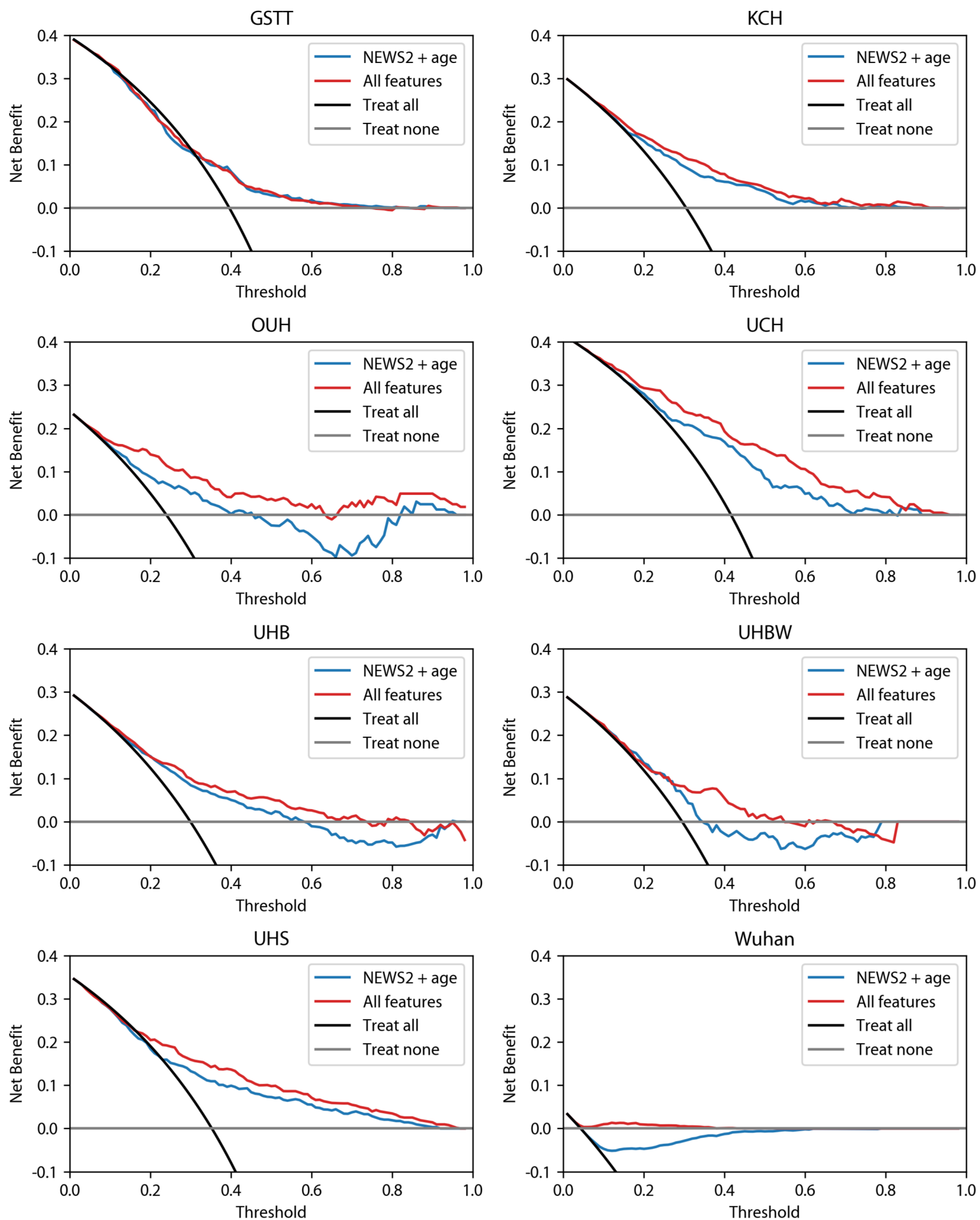


Table 1: Patient characteristics of the training/validation cohorts

	Training cohort		U
	KCH (n=1276)		
COVID-19 WHO Score 6-8 (ICU/death)	N avail.	N (%)	N avail.
3 days	1276	163 (12.8%)	633
14 days	1276	389 (30.5%)	633
Demographics	N avail.	N (%)	N avail.
Age (median [IQR])	1276	71.5 [57.1, 82.6]	633
Sex (male)	1276	742 (58.2%)	633
Non-White ethnicity	960	379 (39.5%)	546
Comorbidities	N avail.	N (%)	N avail.
Hypertension	1276	695 (54.5%)	633
Diabetes mellitus	1276	439 (34.4%)	633
Heart Failure	1276	117 (9.2%)	633
Ischaemic Heart Diseases	1276	185 (14.5%)	633
COPD	1276	141 (11.1%)	633
Asthma	1276	174 (13.6%)	633
Chronic Kidney Disease	1276	234 (18.3%)	633
Blood biomarker	N avail.	Median [IQR]	N avail.
Albumin (g/L)	1153	37.0 [33.0, 40.0]	501
C-reactive protein (CRP, mg/L)	1240	80.0 [36.0, 141.6]	545
Urea (mmol/L)	1221	7.1 [4.6, 11.7]	563
Estimated GFR	1254	65.0 [41.0, 86.0]	377
Haemoglobin (g/L)	1223	127.0 [112.0, 141.0]	561
Lymphocyte count (x10 ⁹ /L)	1221	0.9 [0.7, 1.3]	561
Neutrophil count (x10 ⁹ /L)	1220	5.4 [3.8, 7.7]	560
Neutrophil/lymphocyte ratio	1218	5.6 [3.4, 9.5]	559
Lymphocyte/CRP ratio	1196	1.2 [0.6, 3.2]	559
Platelet count (x10 ⁹ /L)	1224	213.0 [161.8, 274.0]	560
Physiological parameters	N avail.	Median [IQR]	N avail.
NEWS2 Total Score	1262	2.0 [1.0, 4.0]	529
Heart rate	1273	85.0 [75.0, 94.0]	560
Oxygen saturation	1273	96.0 [95.0, 98.0]	561
Oxygen flow rate (L/min)	1271	0.0 [0.0, 4.0]	260
Respiration rate	1273	19.0 [18.0, 21.0]	561
Systolic blood pressure	1273	125.0 [112.0, 139.0]	555
Diastolic blood pressure	1273	71.0 [62.0, 80.0]	555
Temperature	1273	36.9 [36.6, 37.4]	558

Notes.

¹Measured as 'Cardiovascular disease' at UCH because separate measures of 'Heart Failure' were not available.

²Measured as overall 'Heart disease' in Wuhan cohort.

UHS (n=633)	UCH (n=411)		GSTT (n=988)	
N (%)	N avail.	N (%)	N avail.	N (%)
109 (17.2%)	411	120 (29.0%)	988	289 (29.3%)
223 (35.2%)	411	171 (42.0%)	988	391 (39.6%)
N (%)	N avail.	N (%)	N avail.	N (%)
73.0 [56.0, 84.0]	411	66.0 [53.0, 79.0]	988	59.0 [46.0, 75.0]
364 (57.5%)	411	252 (61.0%)	988	581 (58.8%)
55 (10.0%)	390	156 (40.0%)	817	607 (74.3%)
N (%)	N avail.	N (%)	N avail.	N (%)
321 (50.7%)	411	172 (42.0%)	988	309 (31.3%)
163 (25.8%)	411	105 (26.0%)	988	286 (28.9%)
137 (21.6%)	410	--	988	52 (5.3%)
152 (24.0%)	409	108 (26.0%) ¹	--	--
115 (18.2%)	409	27 (6.6%)	988	64 (6.5%)
112 (17.7%)	409	41 (10.0%)	988	85 (8.6%)
111 (17.5%)	410	40 (9.8%)	988	110 (11.1%)
Median [IQR]	N avail.	Median [IQR]	N avail.	Median [IQR]
32.0 [29.0, 36.0]	390	38.0 [35.0, 42.0]	863	36.0 [31.0, 40.0]
75.0 [25.0, 150.0]	403	97.0 [45.0, 179.0]	974	76.5 [25.0, 153.8]
6.95 [4.8, 10.6]	375	6.0 [4.0, 9.4]	489	7.4 [4.6, 12.5]
62.0 [40.0, 81.0]	407	77.0 [54.0, 96.0]	965	74.0 [49.0, 100.0]
128.0 [111.0, 143.0]	410	130.0 [112.0, 143.0]	987	125.0 [108.0, 139.0]
1.0 [0.7, 1.4]	410	0.9 [0.6, 1.4]	987	0.9 [0.6, 1.3]
5.8 [4.2, 8.8]	410	5.9 [3.9, 8.2]	986	5.0 [3.5, 8.1]
5.8 [3.4, 10]	410	6.0 [4.0, 10.0]	986	5.6 [3.2, 10.1]
1.3 [0.5, 4.6]	402	1.0 [0.4, 2.4]		0.0 [0.0, 0.0]
231 [176.8, 303.5]	409	221.0 [169.0, 280.0]	986	209.0 [161.0, 275.8]
Median [IQR]	N avail.	Median [IQR]	N avail.	Median [IQR]
3.0 [2.0, 5.0]	404	5.0 [3.0, 7.0]	744	3.0 [1.0, 5.0]
90.5 [82.0, 102.0]	410	94.0 [81.0, 107.0]	752	85.0 [75.0, 95.0]
97.0 [96.0, 99.0]	410	96.0 [94.0, 98.0]	712	96.0 [95.0, 97.0]
3.0 [2.0, 8.0]	403	2.0 [0.0, 10.0]	978	0.0 [0.0, 0.0]
20.0 [19.0, 24.0]	410	24.0 [20.0, 28.0]	755	19.0 [18.0, 22.0]
137.0 [123.0, 152.0]	411	131.0 [115.0, 143.0]	751	125.0 [115.0, 140.0]
78.0 [70.0, 85.0]	411	73.0 [64.0, 81.0]	751	74.0 [66.0, 81.0]
36.9 [36.7, 37.5]	410	37.3 [36.8, 38.1]	750	36.9 [36.4, 37.5]

lure’ and ‘*Ischaemic Heart Diseases*’ were unavailable.

Validation cohorts (n=6237)				
UHBW (n=190)		Wuhan (n=2815)		U
N avail.	N (%)	N avail.	N (%)	N avail.
190	32 (16.8%)	2815	58 (2.1%)	1037
190	56 (29.5%)	2815	118 (4.2%)	1037
N avail.	N (%)	N avail.	N (%)	N avail.
190	73.5 [59.3, 82.0]	2815	60.0 [50.0, 68.0]	1037
190	120 (63.1%)	2815	1437 (51.0%)	1037
190	46 (24.2%)	2815	2815 (100%)	892
N avail.	N (%)	N avail.	N (%)	N avail.
190	117 (61.6%)	2815	821 (29.2%)	1037
190	71 (37.4%)	2815	371 (13.2%)	1037
190	33 (17.4%)	2815	236 (8.4%) ²	1037
190	52 (27.4%)	--	--	1037
190	41 (21.6%)	2815	17 (0.6%)	1037
190	27 (14.2%)	--	--	1037
190	59 (31.1%)	2815	56 (2.0%)	1037
N avail.	Median [IQR]	N avail.	Median [IQR]	N avail.
190	30.0 [27.0, 33.0]	2404	38.1 [35.1, 40.5]	993
190	77.0 [36.3, 138.3]	2393	2.3 [0.8, 9.0]	970
--	--	--	--	1018
190	68.0 [43.3, 88.0]	2433	103.1 [88.2, 117.5]	757
190	129.0 [110.0, 141.0]	2584	124.0 [113.0, 135.0]	1009
190	0.9 [0.6, 1.2]	2584	1.5 [1.1, 1.9]	1011
190	5.2 [3.5, 7.4]	2584	3.5 [2.7, 4.7]	1011
190	5.7 [3.6, 9.8]	2584	2.3 [1.7, 3.5]	1011
190	1.1 [0.5, 2.7]	2362	0.7 [0.1, 2.0]	962
190	207.5 [150.3, 268.5]	2584	223.0 [179.8, 273.0]	1008
N avail.	Median [IQR]	N avail.	Median [IQR]	N avail.
190	3.0 [2.0, 5.0]	2804	1.0 [0.0, 3.0]	1019
190	82.0 [71.0, 95.0]	2812	81.0 [76.9, 85.8]	1028
190	95.0 [94.0, 96.0]	2797	97.8 [97.0, 98.2]	1029
190	2.0 [0.0, 3.0]	--	--	1017
190	20.0 [18.0, 21.0]	2811	20.0 [19.0, 21.0]	1020
190	123.0 [111.0, 140.8]	1431	120.0 [110.0, 128.0]	1022
190	72.0 [64.3, 82.0]	1433	71.0 [65.0, 78.0]	1022
190	37.2 [36.7, 37.9]	2815	36.5 [36.3, 36.7]	1029

JHB (n=1037)	Oslo (n=163)	
N (%)	N avail.	N (%)
169 (16.3%)	163	27 (16.3%)
310 (29.9%)	163	39 (23.9%)
N (%)	N avail.	N (%)
70.0 [57.0, 82.0]	163	60.0 [48.0-74.0]
573 (55.3%)	163	95 (58.3%)
306 (34.3%)	--	--
N (%)	N avail.	N (%)
637 [61.4%]	163	55 (33.7%)
358 (34.5%)	163	27 (16.6%)
178 (17.2%)	163	15 (9.2%)
245 (23.6%)	163	21 (12.9%)
152 (14.7%)	--	--
169 (16.3%)	--	--
274 (26.4%)	163	9 (5.5%)
Median [IQR]	N avail.	Median [IQR]
32.0 [28.0, 35.0]	120	39.0 [36.0-43.0]
89.0 [33.2, 157.0]	163	48.0 [16.0-113.0]
6.8 [4.6, 11.8]	154	5.5 [4.3-7.5]
54.0 [29.0, 72.0]	163	84.0 [57.0-99.0]
130.0 [113.0, 144.0]	163	139.0[129.0-148.0]
0.9 [0.7, 1.4]	153	1.1 [0.8-1.5]
5.5 [3.8, 8.2]	153	4.4 [3.0-7.1]
5.6 [3.2, 10.2]	153	4.3 [2.4-7.7]
1.1 [0.5, 3.3]	--	--
218.0 [165.0, 287.2]	163	205.0 [160.0-279.0]
Median [IQR]	N avail.	Median [IQR]
4.0 [2.0, 7.0]	163	5.0 [3.0-7.0]
90.0 [79.0, 104.0]	160	89.5 [75.3-100.8]
96.0 [94.0, 98.0]	163	95.0 [92.0-97.0]
0.0 [0.0, 4.0]	125	1.0 [0.0-2.0]
20.0 [18.0, 25.0]	160	24.0 [20.0-28.0]
128.0 [113.0, 144.0]	160	129 [116.0-142.8]
75.0 [67.0, 84.0]	160	77.0 [69.0-87.0]
36.8 [36.2, 37.5]	162	37.2 [36.5-38.3]

Table S1: SNOMED terms

SNOMED concept name	SNOMED concept IDs
Diabetes	S-230572002, S-44054006, S-237599002, S-49455004
Heart Failure	S-42343007, S-426263006, S-48447003, S-418304008, S-10633002
IHD	S-401314000, S-194828000, S-233839009, S-414545008
Hypertension	S-59621000
COPD	S-13645005, S-313297008
Asthma	S-195967001
CKD	S-433144002, S-90688005, S-709044004

Table S2: F1, precision and recall for NLP comorbidity detection

MedCATTrainer was used to collect manual annotations for 146 clinical documents totalling 4343 annotations. Each co-morbidity is defined using one or more SNOMED terms. Predicted true positive labels (TP), precision (P), recall (R), F1-score (F1) are shown for these aggregated concepts. These results only consider entity detection and not meta annotation.

	TP	F1	P	R	SNOMED terms
Diabetes mellitus	73	0.936	0.924	0.948	S-230572002, S-44054006, S-237599002, S-49455004 S-42343007, S-426263006 S-48447003, S-418304008
Heart Failure	11	0.893	0.786	1	S-10633002 S-401314000, S-194828000 S-233839009, S-414545008 S-394659003, S-1755008
IHD	23	0.979	0.958	1	S-413838009
Hypertension	84	0.883	0.988	0.778	S-59621000
COPD	14	0.967	0.933	1	S-13645005, S-313297008
Asthma	11	1	1	1	S-195967001 S-433144002, S-90688005,
CKD	15	0.938	0.938	0.938	S-709044004

Table S3: Logistic regression models for each blood and physiological measure tested separately

	N avail.	14 day ICU/death		
		Model 1: Age, sex only ¹		Model 2: + comorbidities ²
		Odds Ratio [95% C.I.]	<i>P</i> -value ³	Odds Ratio [95% C.I.]
NEWS2 score	1262	2.10 [1.83, 2.40]	<0.001	2.13 [1.86, 2.44]
Oxygen flow rate	1271	1.92 [1.70, 2.17]	<0.001	1.97 [1.74, 2.22]
Respiratory rate	1273	1.65 [1.45, 1.86]	<0.001	1.65 [1.45, 1.87]
CRP	1240	1.64 [1.44, 1.87]	<0.001	1.65 [1.45, 1.88]
Lymphocyte/CRP ratio	1196	0.63 [0.55, 0.73]	<0.001	0.63 [0.54, 0.72]
Oxygen saturation	1273	0.65 [0.57, 0.73]	<0.001	0.63 [0.56, 0.72]
Neutrophil count	1220	1.41 [1.25, 1.60]	<0.001	1.42 [1.25, 1.61]
Urea	1221	1.40 [1.23, 1.60]	<0.001	1.42 [1.23, 1.64]
Neutrophil/lymphocyte ratio	1218	1.38 [1.21, 1.57]	<0.001	1.39 [1.21, 1.58]
Heart rate	1273	1.34 [1.18, 1.52]	<0.001	1.35 [1.19, 1.53]
Estimated GFR	1254	0.78 [0.68, 0.88]	<0.001	0.76 [0.66, 0.88]
Albumin	1153	0.80 [0.70, 0.92]	0.002	0.81 [0.71, 0.92]
Temperature	1273	1.21 [1.07, 1.37]	0.004	1.21 [1.07, 1.38]
Platelet count	1224	0.88 [0.78, 1.01]	0.075	0.88 [0.78, 1.01]
Diastolic blood pressure	1273	0.89 [0.78, 1.00]	0.075	0.89 [0.78, 1.01]
Systolic blood pressure	1273	0.91 [0.81, 1.03]	0.157	0.91 [0.80, 1.03]
Lymphocytes	1221	0.93 [0.82, 1.06]	0.279	0.93 [0.82, 1.06]
Hemoglobin	1223	1.04 [0.92, 1.19]	0.505	1.07 [0.94, 1.22]

Notes.

Continuous predictors were standardised (mean = 0; standard deviation = 1), therefore, odds ratio each tested in a separate model. ¹Adjusted for age and sex only. ²Additionally adjusted for comorbidities (chronic kidney disease). ³FDR-corrected *P*-values based on the Benjamini-Hochberg correction.

ately in the KCH training cohort, for 14- and 3-day ICU/death

3 day ICU/death				
rbidities ²	Model 1: Age, sex only ¹		Model 2: + comorbidities ²	
	Odds Ratio		Odds Ratio	
<i>P-value</i> ³	[95% C.I.]	<i>P-value</i> ³	[95% C.I.]	<i>P-value</i> ³
<0.001	2.66 [2.25, 3.16]	<0.001	2.65 [2.23, 3.15]	<0.001
<0.001	2.22 [1.92, 2.56]	<0.001	2.25 [1.94, 2.60]	<0.001
<0.001	1.83 [1.59, 2.10]	<0.001	1.81 [1.58, 2.09]	<0.001
<0.001	1.89 [1.59, 2.24]	<0.001	1.92 [1.61, 2.28]	<0.001
<0.001	0.58 [0.47, 0.71]	<0.001	0.57 [0.47, 0.71]	<0.001
<0.001	0.51 [0.44, 0.60]	<0.001	0.49 [0.42, 0.58]	<0.001
<0.001	1.53 [1.31, 1.80]	<0.001	1.54 [1.31, 1.81]	<0.001
<0.001	1.38 [1.17, 1.63]	<0.001	1.48 [1.23, 1.78]	<0.001
<0.001	1.44 [1.21, 1.73]	<0.001	1.45 [1.21, 1.74]	<0.001
<0.001	1.54 [1.30, 1.82]	<0.001	1.54 [1.30, 1.82]	<0.001
<0.001	0.87 [0.73, 1.03]	0.125	0.82 [0.67, 1.00]	0.058
0.002	0.76 [0.64, 0.90]	0.002	0.75 [0.63, 0.89]	0.002
0.003	1.23 [1.04, 1.44]	0.018	1.23 [1.05, 1.45]	0.016
0.080	1.05 [0.89, 1.24]	0.630	1.04 [0.88, 1.23]	0.698
0.080	0.80 [0.67, 0.95]	0.016	0.79 [0.66, 0.94]	0.012
0.148	0.95 [0.80, 1.13]	0.625	0.94 [0.79, 1.12]	0.522
0.282	1.01 [0.85, 1.19]	0.942	1.00 [0.84, 1.19]	0.980
0.329	1.20 [1.01, 1.44]	0.052	1.21 [1.00, 1.45]	0.057

os represent one standard deviation change in the respective parameter,
rbidities (hypertension, diabetes, heart diseases, respiratory diseases and

Table S4: Internally validated discrimination for KCH training sample based on nested

Outcome	Sample	Model	No. features
14-day ICU/death ¹	Subset 1: Patients with data on ethnicity (n=960)	NEWS2 + age	2
		All features	9
	Subset 2: Excluding nosocomial patients (n=1123)	NEWS2 + age	2
		All features	9
3-day ICU/death ²	All patients (n=1276)	NEWS2 + age	2
		All features	2
	Subset 1: Patients with non-missing ethnicity (n=960)	NEWS2 + age	2
		All features	2
	Subset 2: Excluding nosocomial patients (n=1123)	NEWS2 + age	2
		All features	2

Notes.

¹ Sensitivity/specificity calculated at 30% probability threshold;

² Calculated at 20% probability threshold.

AUC based on repeated, nested cross-validation (inner loop: 10 folds; outer loop = 10 folds/1000 repeats).

Missing values imputed at each outer loop with k-Nearest Neighbours (KNN) imputation.

ed repeated cross-validation

AUC [95% CI]	Brier score [95% CI]	Sensitivity [95% CI]	Specificity [95% CI]
0.694 [0.667, 0.721]	0.197 [0.191, 0.204]	0.848 [0.811, 0.889]	0.364 [0.324, 0.405]
0.728 [0.703, 0.754]	0.189 [0.183, 0.195]	0.806 [0.768, 0.845]	0.496 [0.459, 0.533]
0.721 [0.701, 0.744]	0.189 [0.184, 0.195]	0.809 [0.775, 0.842]	0.474 [0.444, 0.507]
0.748 [0.727, 0.770]	0.183 [0.177, 0.188]	0.780 [0.743, 0.815]	0.539 [0.503, 0.571]
0.764 [0.737, 0.794]	0.114 [0.108, 0.120]	0.967 [0.871, 1.000]	0.286 [0.000, 0.461]
0.789 [0.763, 0.819]	0.110 [0.103, 0.116]	0.856 [0.793, 0.933]	0.534 [0.475, 0.617]
0.763 [0.732, 0.796]	0.114 [0.107, 0.122]	0.958 [0.857, 1.000]	0.363 [0.211, 0.473]
0.774 [0.740, 0.810]	0.110 [0.102, 0.118]	0.838 [0.739, 0.950]	0.578 [0.429, 0.669]
0.769 [0.738, 0.798]	0.119 [0.113, 0.126]	1.000 [0.971, 1.000]	0.150 [0.000, 0.187]
0.796 [0.767, 0.825]	0.115 [0.108, 0.122]	0.940 [0.888, 1.000]	0.343 [0.180, 0.483]

NEWS2 + age

All features

Observed proportion

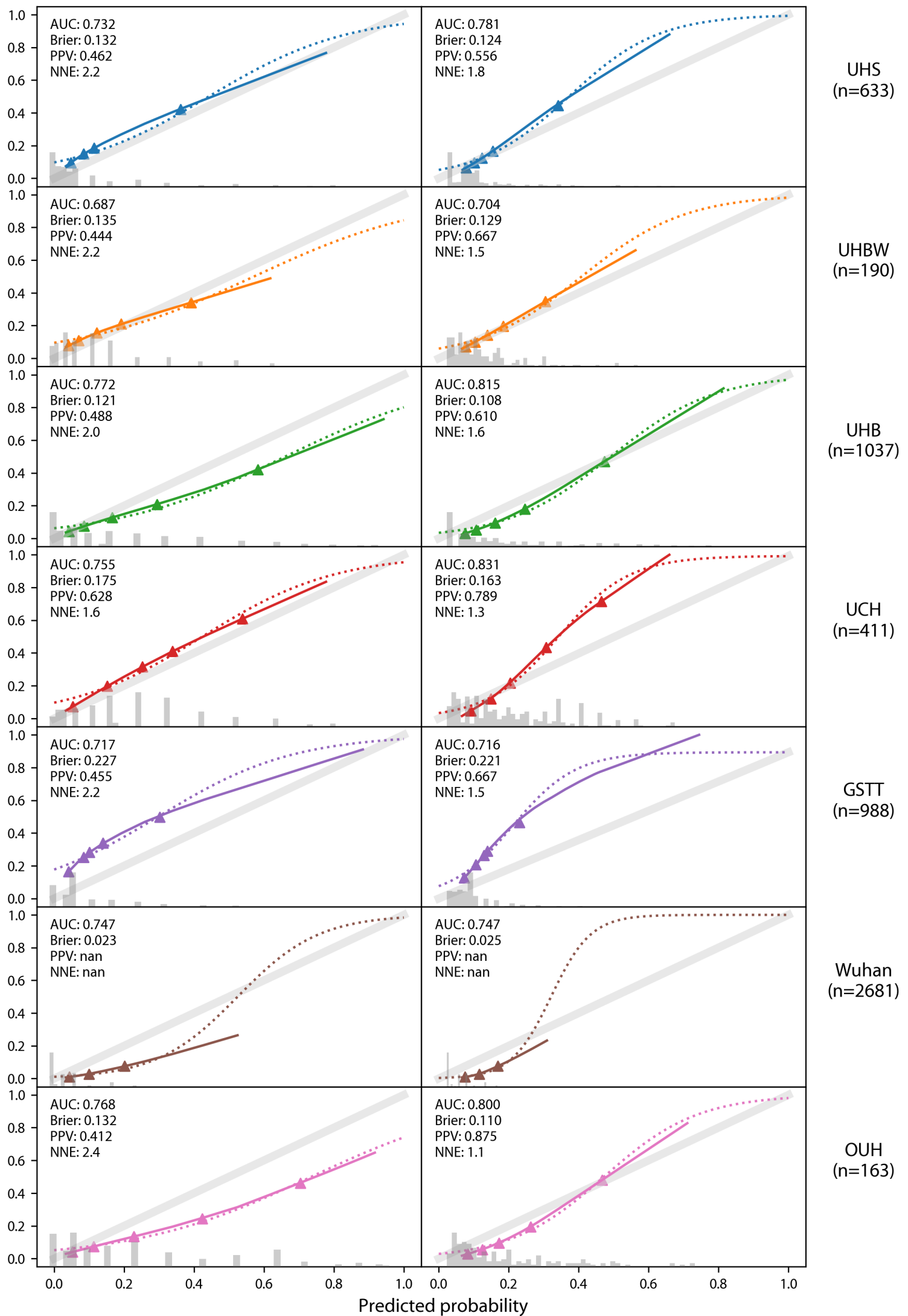


Table S5: Univariate logistic regression models for sensitivity analyses showing odds ratios of
14-day ICU/death

	Subset 1: Adjusted for ethnicity, in the subset of patients with non-missing ethnicity			Subset 2: Excluding nosc patients	
	N	OR [95% CI]	P-value	N	OR [95% CI]
NEWS2 score	948	2.07 [1.78, 2.41]	<0.001	1109	2.27 [1.96, 2.63]
Oxygen flow rate	955	1.80 [1.57, 2.07]	<0.001	1118	2.01 [1.77, 2.29]
Oxygen saturation	957	0.60 [0.51, 0.69]	<0.001	1120	0.63 [0.55, 0.72]
CRP	932	1.71 [1.47, 1.99]	<0.001	1092	1.61 [1.40, 1.85]
Respiratory rate	957	1.61 [1.40, 1.85]	<0.001	1120	1.66 [1.46, 1.89]
Lymphocyte/CRP ratio	900	0.59 [0.50, 0.71]	<0.001	1056	0.64 [0.55, 0.75]
Heart rate	957	1.36 [1.18, 1.56]	<0.001	1120	1.39 [1.22, 1.59]
Neutrophil count	918	1.49 [1.29, 1.73]	<0.001	1075	1.34 [1.17, 1.54]
Neutrophil/lymphocyte ratio	917	1.47 [1.26, 1.71]	<0.001	1074	1.33 [1.15, 1.53]
Urea	917	1.38 [1.17, 1.62]	<0.001	1084	1.36 [1.17, 1.58]
Albumin	866	0.81 [0.69, 0.94]	0.008	1036	0.80 [0.68, 0.93]
Diastolic blood pressure	957	0.91 [0.79, 1.05]	0.22	1120	0.88 [0.77, 1.00]
Temperature	957	1.22 [1.06, 1.41]	0.008	1120	1.28 [1.12, 1.46]
Hemoglobin	921	1.07 [0.92, 1.25]	0.374	1079	1.11 [0.95, 1.28]
Estimated GFR	944	0.80 [0.69, 0.93]	0.003	1108	0.78 [0.68, 0.90]
Systolic blood pressure	957	0.90 [0.78, 1.04]	0.177	1120	0.93 [0.82, 1.06]
Platelet count	922	0.88 [0.76, 1.03]	0.134	1079	0.92 [0.79, 1.06]
Lymphocytes	920	0.93 [0.81, 1.07]	0.281	1076	0.92 [0.81, 1.05]

Notes.

All models in this table are adjusted for age, sex, and comorbiddities.

f ICU/death at 3- and 14-days for subsets of the training cohort

nosocomial	3-day ICU/death					
	Subset 1: Adjusted for ethnicity, in the subset of patients with non-missing ethnicity			Subset 2: Excluding nosocomial patients		
P-value	N	OR [95% CI]	P-value	N	OR [95% CI]	P-value
<0.001	948	2.50 [2.06, 3.03]	<0.001	1109	2.75 [2.29, 3.31]	<0.001
<0.001	955	2.12 [1.80, 2.50]	<0.001	1118	2.30 [1.97, 2.67]	<0.001
<0.001	957	0.47 [0.39, 0.57]	<0.001	1120	0.51 [0.43, 0.60]	<0.001
<0.001	932	1.97 [1.60, 2.42]	<0.001	1092	1.86 [1.55, 2.23]	<0.001
<0.001	957	1.68 [1.43, 1.96]	<0.001	1120	1.85 [1.60, 2.14]	<0.001
<0.001	900	0.58 [0.46, 0.74]	<0.001	1056	0.60 [0.48, 0.74]	<0.001
<0.001	957	1.59 [1.31, 1.92]	<0.001	1120	1.53 [1.29, 1.83]	<0.001
<0.001	918	1.63 [1.35, 1.97]	<0.001	1075	1.55 [1.30, 1.85]	<0.001
<0.001	917	1.50 [1.21, 1.85]	<0.001	1074	1.41 [1.16, 1.71]	<0.001
<0.001	917	1.41 [1.15, 1.74]	0.002	1084	1.43 [1.18, 1.73]	<0.001
0.005	866	0.75 [0.61, 0.92]	0.009	1036	0.69 [0.56, 0.84]	<0.001
0.071	957	0.80 [0.65, 0.99]	0.056	1120	0.77 [0.64, 0.93]	0.01
<0.001	957	1.19 [0.99, 1.43]	0.082	1120	1.22 [1.03, 1.44]	0.025
0.215	921	1.23 [1.00, 1.52]	0.071	1079	1.19 [0.97, 1.45]	0.116
0.005	944	0.92 [0.75, 1.12]	0.137	1108	0.87 [0.72, 1.04]	0.116
0.282	957	0.95 [0.78, 1.15]	0.615	1120	0.98 [0.82, 1.17]	0.821
0.271	922	1.12 [0.93, 1.36]	0.265	1079	1.14 [0.95, 1.37]	0.167
0.222	920	1.04 [0.86, 1.27]	0.727	1076	1.04 [0.87, 1.24]	0.778

Table S6: Discrimination for all models in training and validation cohorts, including alternative bas

Cohort	Endpoint	Model	AUC	Sens. ¹	Spec. ¹
Training	KCH ²	NEWS2 only	0.760	0.971	0.301
		3 days			
		NEWS2 + age	0.764	0.967	0.286
		All features	0.789	0.856	0.534
		NEWS2 only	0.672	1.000	0.000
		14 days			
		NEWS2 + age	0.700	0.778	0.478
		All features	0.735	0.735	0.592
	UHB	NEWS2 only	0.772	0.361	0.926
		3 days			
		NEWS2 + age	0.772	0.361	0.926
		All features	0.815	0.296	0.963
		NEWS2 only	0.734	0.465	0.839
		14 days			
		NEWS2 + age	0.728	0.532	0.799
		All features	0.771	0.594	0.821
	UCH	NEWS2 only	0.755	0.225	0.945
		3 days			
		NEWS2 + age	0.755	0.225	0.945
		All features	0.831	0.125	0.986
		NEWS2 only	0.697	0.474	0.817
		14 days			
		NEWS2 + age	0.729	0.503	0.788
		All features	0.809	0.509	0.896
Validation	GSTT	NEWS2 only	0.717	0.035	0.983
		3 days			
		NEWS2 + age	0.717	0.035	0.983
		All features	0.716	0.007	0.999
		NEWS2 only	0.734	0.123	0.972
		14 days			
		NEWS2 + age	0.686	0.156	0.946
		All features	0.762	0.136	0.972
	OUH	NEWS2 only	0.768	0.519	0.853
		3 days			
		NEWS2 + age	0.768	0.519	0.853
		All features	0.800	0.259	0.993
		NEWS2 only	0.759	0.641	0.790
		14 days			
		NEWS2 + age	0.786	0.615	0.774
		All features	0.837	0.564	0.871
	UHBW	NEWS2 only	0.687	0.125	0.968
		3 days			
		NEWS2 + age	0.687	0.125	0.968
		All features	0.704	0.063	0.994
		NEWS2 only	0.632	0.143	0.888
		14 days			
		NEWS2 + age	0.623	0.250	0.858
		All features	0.693	0.286	0.903
	UHS	NEWS2 only	0.732	0.110	0.973
		3 days			
		NEWS2 + age	0.732	0.110	0.973
		All features	0.781	0.092	0.985
		NEWS2 only	0.743	0.202	0.988
		14 days			
		NEWS2 + age	0.710	0.251	0.976

Wuhan	3 days	All features	0.770	0.345	0.963
		NEWS2 only	0.747	0.000	1.000
		NEWS2 + age	0.747	0.000	1.000
		All features	0.747	0.000	1.000
		NEWS2 only	0.744	0.035	0.996
		NEWS2 + age	0.815	0.122	0.988
	14 days	All features	0.864	0.009	1.000

Notes.

AUC = Area Under the Receiver Operating Characteristic curve; TP = true positives; TN = true negatives; FN = false negatives; Sens. = Sensitivity; Spec. = Specificity; PPV = Positive Predictive Value.

¹ Thresholds for sensitivity and specificity were 20% and 30% for 3-day and 14-day endpoints, respectively.

² Estimates for KCH derived from internal cross-validation.

baseline model of ‘NEWS2 only’.

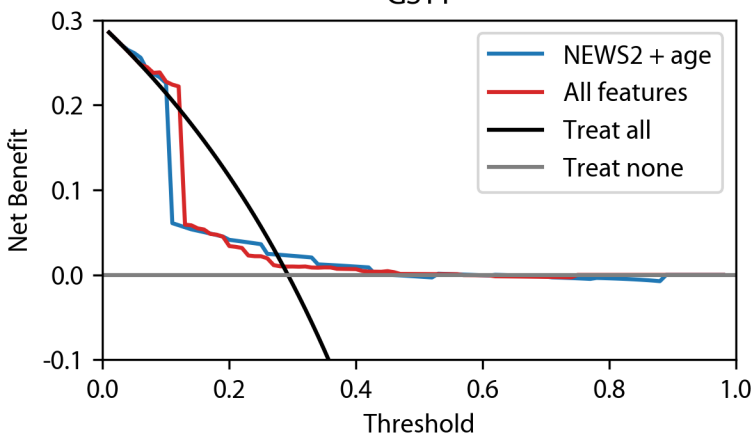
Brier score	N
0.114	1276
0.114	1276
0.110	1276
0.217	1276
0.192	1276
0.183	1276
0.121	1037
0.121	1037
0.108	1037
0.188	1037
0.193	1037
0.176	1037
0.175	411
0.175	411
0.163	411
0.214	411
0.205	411
0.178	411
0.227	988
0.227	988
0.221	988
0.222	988
0.231	988
0.229	988
0.132	163
0.132	163
0.110	163
0.192	163
0.177	163
0.137	163
0.135	190
0.135	190
0.129	190
0.207	190
0.211	190
0.189	190
0.132	633
0.132	633
0.124	633
0.192	633
0.195	633

0.177	633
0.979	2681
0.979	2681
0.979	2681
0.076	2681
0.062	2681
0.037	2681

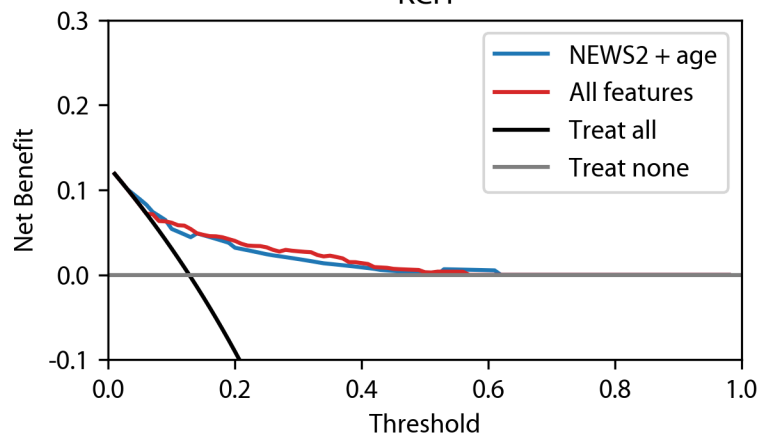
gatives; FP = false

Value; NPV = Negative

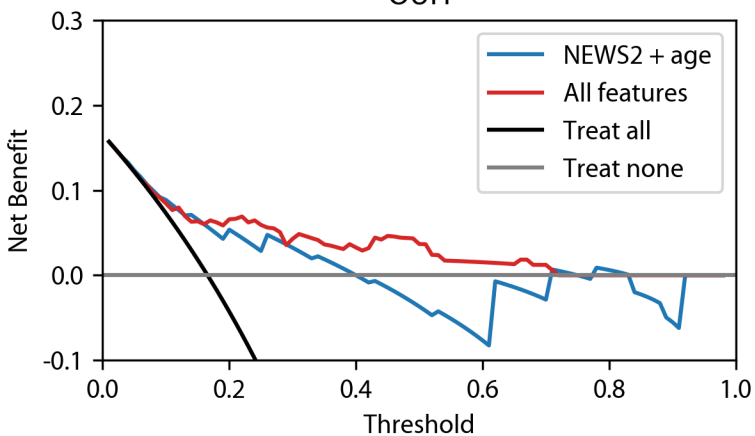
GSTT



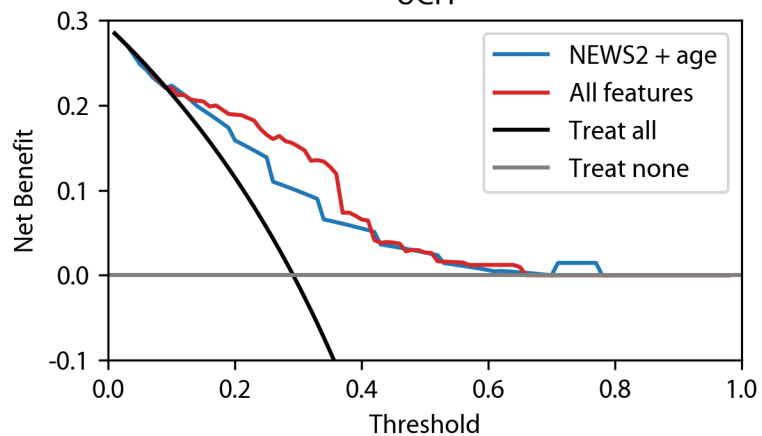
KCH



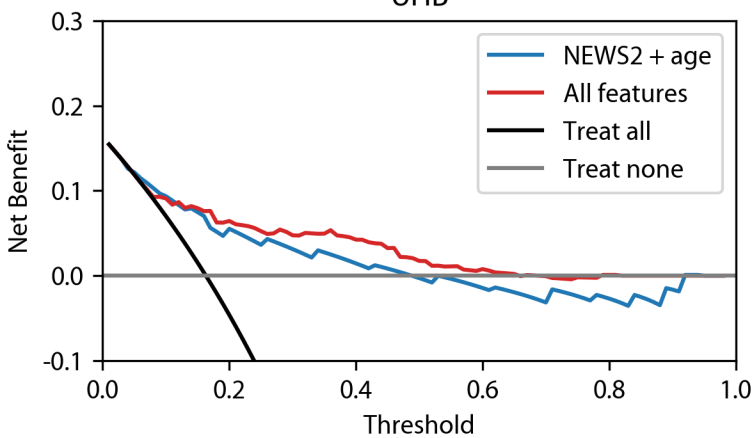
OUH



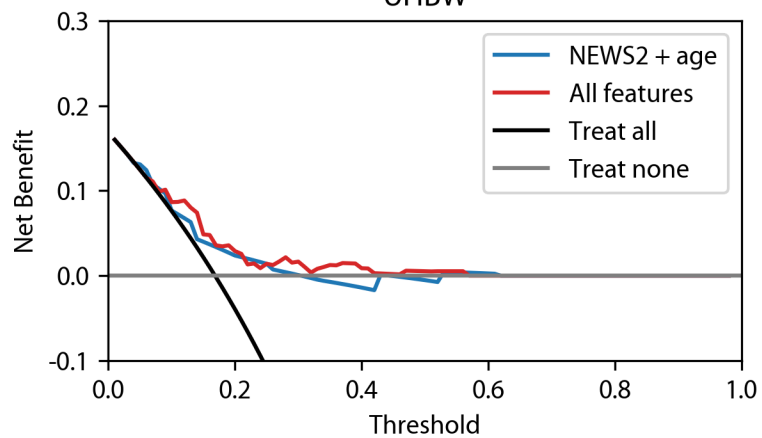
UCH



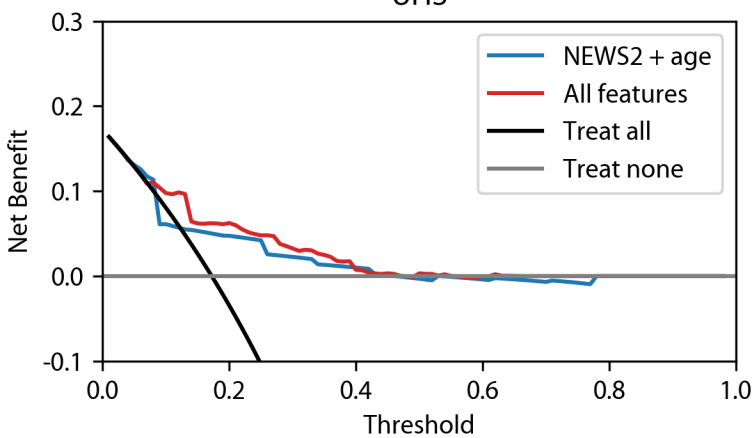
UHB



UHBW



UHS



Wuhan

